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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,000	09/26/2003	Anne Skaja Robinson	00131-00350-USU	9773

23416 7590 06/30/2006

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EXAMINER	
TRAN, MY CHAU T	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/673,000	ROBINSON ET AL.	
	Examiner	Art Unit	
	MY-CHAU T. TRAN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03/03/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application and Claims Status

1. Applicant's response filed 03/28/2006 is acknowledged and entered.

2. The preliminary amendment filed on 03/03/2004 submitted replacement drawing sheets.

3. The preliminary amendment filed on 09/26/2003 amended the specification to include a specific reference to a previously filed application in order to comply with one of the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. In addition the examiner has request clarification regarding the issue as to whether the claims were also amended as indicated in the filed preliminary amendment, applicant response is that '*the preliminary amendment filed 09/26/2003 erroneously indicated that the claims were being amended.* ***Thus, no amendment of the claims was requested.***'

4. Claims 1-18 are pending.

Election/Restrictions

5. Applicant's election of Group I (Claims 7-12) in the reply filed on 03/28/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In addition as indicated in the restriction requirement mailed 02/24/2006, claims 1-6 are linking claims and will be examined with the elected invention of claims 7-12.

6. Claims 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to ***a nonelected invention***, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/28/2006.

Priority

7. This instant application is a DIV of 09/695,762 filed 10/25/2000, which claims benefit to a provisional application of 60/161,035 filed 10/25/1999.

However, only claims 1-2, 7, and 9 are granted the benefit of priority for 09/695,762 under 35 U.S.C. 120 and for 60/161,035 under 35 U.S.C. 119(e) because claims 3-12 are directed to subject matter not adequately disclosed under 35 USC 112, first paragraph, in the parent application, i.e. 09/695,762. For example, claim 3 recites the limitation of "*wherein said elevated hydrostatic pressure is insufficient to fully denature said protein*" that has no support in the specification and original claims of the parent application, i.e. 09/695,762. Claim 8 recites the limitation of "*wherein said elevated hydrostatic pressure is insufficient to fully denature said protein folding intermediates*" that has no support in the specification and original claims of the parent application, i.e. 09/695,762. As a result, the claims 3-6 and 8-12 are only granted the effective filing date of 09/26/2003.

Furthermore, claims 3-6, 8, and 10-12 are considered as continuation-in-part (CIP), ***but*** this application as filed is an improper continuation-in-part (CIP) application because a CIP application requires a newly executed oath or declaration. Here, the declaration filed is a copy of the executed oath or declaration filed in the prior application, i.e. 09/695,762. See 37 C.F.R.

1.63(e). Thus with regard to claims 3-6, 8, and 10-12, this application as filed is an improper continuation-in-part (CIP) application.

Information Disclosure Statement

8. The information disclosure statements (IDS) filed on 03/03/2004 have been reviewed, and the references that have been considered are initialed as recorded in PTO-1449 forms. *Note: Applicant indicated that copies of the documents were submitted in the parent application of 09/695,762.*

9. Claims 1-12 are under consideration in this Office Action.

Specification

10. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter of claims 3-6, 8, and 10-12. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: For example, claim 3 recites the limitation of "*wherein said elevated hydrostatic pressure is insufficient to fully denature said protein*" which has no clear antecedent basis in the instant specification. Claim 8 recites the limitation of "*wherein said elevated hydrostatic pressure is insufficient to fully denature said protein folding intermediates*" that has no clear antecedent basis in the instant specification. The instant specification disclosure is directed to the high hydrostatic pressure range to which the protein is subjected (see specification pg. 9, lines 9-12) and the protein is denature prior to application of

high hydrostatic pressure (see specification pg. 9, lines 13-28; pg. 17, lines 19-28). Thus, the limitations of claims 3-6 and 8-12 have no clear antecedent basis in the instant specification.

Claim Objections

11. Claims 3, 5, 8, and 11 are objected to because of the following informalities: Claims 3, 5, 8, and 11 recite the term "hydrostic". This term appears to be a misspelling of the term "hydrostatic" recited in both claim 1 and 7. Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant invention recites a method for recovering native protein from a sample. The method comprises the steps of:

a) obtaining a sample comprising protein aggregates;

b) subjecting the sample of step (a) to elevated hydrostatic pressure, whereby a portion of protein dissociates from said protein aggregates; and

c) returning the sample of step (b) to ambient pressure, whereby a portion of the dissociated protein refolds to native protein.

With regard to the written description requirement, the attention of the Applicant is directed *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985)(quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Additionally, it is noted that written description is legally distinct from enablement: "Although the two concepts are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.* And also *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

In this instant case, the instant invention claimed a method that uses a broad genus of compositions, i.e. protein aggregates, which represents enormous scope because the claims do not place any limitations on the number of atoms, i.e. binding moieties, types of atoms or the way in which said atoms can be connected together to form such a compound and/or composition (protein structures). For example, Lehninger et al. disclose each protein has a specific chemical or structural function such that each protein has a unique three-dimensional structure (pg. 160, lines 4-6; fig. 7-1). The three-dimensional structure of a protein is determined by its amino acid, but the relationship between the amino acid sequence and the three-dimensional structure is an intricate puzzle that has yet to be solved in detail (see pg. 160, lines 14-29). Thus, virtually an infinite number of possibilities would be included in Applicants' claimed scope encompassing virtually every known class and subclass of compounds, i.e. the protein structures of the folding and aggregates pathway for any protein.

In addition, the instant claimed protein aggregates is further define by a functional limitations, i.e. '*a portion of protein dissociates from said protein aggregates*' at high pressure, which does not alleviate these deficiencies. The CFC has also stated that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials" (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993)). Here, applicants have failed to provide an 'explicit' definition, structure, formula or chemical name for any of the instant claimed composition, i.e. protein aggregates. In addition, the CAFC has stated that a genus, which is set forth only in functional term, "...is not

an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g. see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997)). Applicants provide no chemical structure for the claimed genus of composition, i.e. protein aggregates, and only distinguish the claimed genus from others, except by function, i.e. '*a portion of protein dissociates from said protein aggregates*' at high pressure. For example, while the methods for pressure denaturation of proteins are known at the time of filing such methods were not sufficiently routine or predictable at the time of filing, to permit one of skill in the art to devise strategies for the use of any protein aggregates such that '*a portion of protein dissociates from said protein aggregates*' at high pressure. For example, Panick et al. disclose the protein structure produced by pressure depends on the type of protein use as the starting material (see pg. 390, left col., line 40 thru right col., lines 19). Moreover, the nature of the transition state(s) in denaturalization of a protein may vary because '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure. For example, it is not known to what extent the structures of the heat and cold denatured proteins are similar. Moreover, our grasp of these possible differences depends upon the observable parameters used, and quantitative comparison of results between techniques is often difficult. Recognizing that the denatured state achieved by any perturbation method likely corresponds to a relatively large ensemble of conformations*' (see pg. 397, left col., line16 thru right col., line 6). Therefore, the art of denaturation of proteins is known to be difficult to optimize and/or correlates, especially when '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure*' (see pg. 397, left col., lines 16-18).

Additionally, *Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc.*, No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

Consequently, the scope of the instant claimed compositions, i.e. protein aggregates, includes an enormous number of structural variants.

In contrast, the instant specification disclosure provided a generic definition of the phrase "protein aggregates" (see specification pg. 7, lines 9-12) and a laundry list as to the type of protein that can be use in the instant claimed method (see specification pg. 10, lines 10-19). The instant specification one example is directed to the method of high-pressure dissociation of protein aggregates intermediate forms using a known protein, i.e. tailspike protein, wherein the intermediate forms of the folding and aggregates pathway of the protein are 'separated' (i.e. '*a portion of protein dissociates from said protein aggregates*' at high pressure)(see specification Example 5, pg. 20, lines 14-26). Moreover, the instant specification discloses that the tailspike protein of P22 bacteriophage is "*an excellent model system for aggregation because the structure is known, the folding and aggregation pathways are well characterized*". Thus, the instant specification one example utilizes a well-known protein in which the intermediate forms of the folding and aggregates pathway of the protein are known.

Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22,

1997; No. 96-1175) regarding adequate disclosure. For adequate disclosure, like enablement, requires ***representative examples***, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. In addition, when there is ***substantial variation within the genus***, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05).

Here, the instant specification has only provided one working example of the claimed invention (i.e. the high-pressure dissociation method using well known tailspike protein wherein the known intermediate forms of the folding and aggregates pathway of the protein are 'separated'). Thus, a person of skill in the art would not believe that Applicants were in possession of a genus that encompasses virtually an infinite number of compounds and/or compositions encompassing every class and subclass of the instant claimed protein aggregates, i.e. the protein structures of the folding and aggregates pathway for any protein.

Accordingly, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention. The instant specification and claims do not provide any guidance as to what changes should be made to extend the instant specification one example to the infinite number of possibilities that are currently being claimed composition, i.e. protein aggregates, for use in the instant claimed method. The general knowledge and level of

skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variable, the instant specification single example is insufficient to describe the enormous genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In the present instance, the specification does not teach claimed method using any protein aggregates. Therefore, only the method of high-pressure dissociation of protein aggregates intermediate forms using a tailspike protein of P22 bacteriophage wherein the known intermediate forms of the folding and aggregates pathway of the protein are 'separated', but not the full breadth of the claim method meet the written description provision of 35 U.S.C 112, first paragraph.

14. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of high-pressure dissociation of protein aggregates intermediate forms using a tailspike protein of P22 bacteriophage wherein the known intermediate forms of the folding and aggregates pathway of the protein are 'separated', does not reasonably provide enablement for the method of high-pressure dissociation of protein aggregates intermediate forms using any type of protein aggregates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is an enablement rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to: 1) The breadth of the claims; 2) The nature of the invention; 3) The state of the prior art; 4) The level of one of ordinary skill; 5) The level of predictability in the art; 6) The amount of direction provided by the inventor; 7) The presence or absence of working examples; and 8) The quantity of experimentation necessary needed to make or use the invention based on the disclosure. (See *In re Wands* USPQ 2d 1400 (CAFC 1988)).

(1-2) The breadth of the claims and the nature of the invention:

The claims are drawn to a broad genus. Here, the instant invention claimed a method that uses a broad genus of compositions, i.e. protein aggregates, which represents enormous scope because the claims do not place any limitations on the number of atoms, i.e. binding moieties, types of atoms or the way in which said atoms can be connected together to form such a

compound and/or composition (protein structures). For example, Lehninger et al. disclose each protein has a specific chemical or structural function such that each protein has a unique three-dimensional structure (pg. 160, lines 4-6; fig. 7-1). The three-dimensional structure of a protein is determined by its amino acid, but the relationship between the amino acid sequence and the three-dimensional structure is an intricate puzzle that has yet to be solved in detail (see pg. 160, lines 14-29). Thus, virtually an infinite number of possibilities would be included in Applicants' claimed scope encompassing virtually every known class and subclass of compounds, i.e. the protein structures of the folding and aggregates pathway for any protein. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art:

The art is unpredictable because while the methods for pressure denaturation of proteins are known at the time of filing such methods were not sufficiently routine or predictable at the time of filing, to permit one of skill in the art to devise strategies for the use of any protein aggregates such that '*a portion of the dissociated protein folding intermediates refolds to native protein*' at high pressure. For example, Panick et al. disclose the protein structure produced by pressure depends on the type of protein use as the starting material (see pg. 390, left col., line 40 thru right col., lines 19). Moreover, the nature of the transition state(s) in denaturalization of a protein may vary because '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure. For example, it is not known to what extent the structures of the heat and cold denatured proteins are similar. Moreover, our grasp of these possible differences depends upon the observable parameters used, and quantitative*

comparison of results between techniques is often difficult. Recognizing that the denatured state achieved by any perturbation method likely corresponds to a relatively large ensemble of conformations' (see pg. 397, left col., line16 thru right col., line 6). Therefore, the art of denaturation of proteins is known to be difficult to optimize and/or correlates, especially when '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure*' (see pg. 397, left col., lines 16-18).

(4) The level of one of ordinary skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples:

Applicants have not provided one example is directed to the method of high-pressure dissociation of protein aggregates intermediate forms using a known protein, i.e. tailspike protein, wherein the intermediate forms of the folding and aggregates pathway of the protein are 'separated' (i.e. '*a portion of protein dissociates from said protein aggregates*' at high pressure)(see specification Example 5, pg. 20, lines 14-26). Moreover, the instant specification discloses that the tailspike protein of P22 bacteriophage is "*an excellent model system for aggregation because the structure is known, the folding and aggregation pathways are well characterized*". Thus, the instant specification one example utilizes a well-known protein in which the intermediate forms of the folding and aggregates pathway of the protein are known.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Therefore based on the evidences as a whole regarding each of the above factors (e.g. factors 1-8), the specification, at the time the application was filed, does not satisfy the enablement requirement for the instant claimed method of high-pressure dissociation of protein aggregates intermediate forms using any type of protein aggregates.

15. Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant invention recites a method for recovering native protein from a sample. The method comprises the steps of:

a) obtaining a sample comprising protein aggregates, wherein said protein aggregates are comprised of protein folding intermediates of a native protein;

b) subjecting the sample of step (a) to elevated hydrostatic pressure, whereby a portion of said protein folding intermediates dissociates from said protein aggregates; and

c) returning the sample of step (b) to ambient pressure, whereby a portion of the dissociated protein folding intermediates refolds to native protein.

With regard to the written description requirement, the attention of the Applicant is directed *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985)(quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Additionally, it is noted that written description is legally distinct from enablement: "Although the two concepts are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the

enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.* And also *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

In this case, the instant invention claimed method uses a broad genus of compositions, i.e. protein aggregates comprising '*protein folding intermediates of a native protein*', which represents enormous scope because the claims do not place any limitations on the number of atoms, i.e. binding moieties, types of atoms or the way in which said atoms can be connected together to form such a compound and/or composition (protein structures). Thus, virtually an infinite number of possibilities would be included in Applicants' claimed scope encompassing virtually every known class and subclass of compounds (protein structures). For example, Lehninger et al. disclose each protein has a specific chemical or structural function such that each protein has a unique three-dimensional structure (pg. 160, lines 4-6; fig. 7-1). The three-dimensional structure of a protein is determined by its amino acid, but the relationship between the amino acid sequence and the three-dimensional structure is an intricate puzzle that has yet to be solved in detail (see pg. 160, lines 14-29). Thus, virtually an infinite number of possibilities would be included in Applicants' claimed scope encompassing virtually every known class and subclass of compounds, i.e. the protein structures of the folding and aggregates pathway for any protein.

In addition, the instant claimed protein aggregates is further define by a functional limitations, i.e. '*a portion of the dissociated protein folding intermediates refolds to native*

protein' which does not alleviate these deficiencies. The CFC has also stated that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials" (e.g., see University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)). Here, applicants have failed to provide a definition, structure, formula or chemical name for any of the instant claimed composition, i.e. self-assembled monolayers (SAMs). In addition, the CAFC has stated that a genus, which is set forth only in functional term, "...is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g. see University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997)). Applicants provide no chemical structure for the claimed genus of composition, i.e. protein aggregates, and only distinguish the claimed genus from others, except by function, i.e. '*a portion of the dissociated protein folding intermediates refolds to native protein*' at high pressure. For example, while the methods for pressure denaturation of proteins are known at the time of filing such methods were not sufficiently routine or predictable at the time of filing, to permit one of skill in the art to devise strategies for the use of any protein aggregates such that '*a portion of the dissociated protein folding intermediates refolds to native protein*' at high pressure. For example, Panick et al. disclose the protein structure produced by pressure depends on the type of protein use as the starting material (see pg. 390, left col., line 40 thru right col., lines 19). Moreover, the nature of the transition state(s) in denaturalization of a protein may vary because '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure. For example, it is not known to what*

extent the structures of the heat and cold denatured proteins are similar. Moreover, our grasp of these possible differences depends upon the observable parameters used, and quantitative comparison of results between techniques is often difficult. Recognizing that the denatured state achieved by any perturbation method likely corresponds to a relatively large ensemble of conformations' (see pg. 397, left col., line16 thru right col., line 6). Therefore, the art of denaturation of proteins is known to be difficult to optimize and/or correlates, especially when '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure*' (see pg. 397, left col., lines 16-18).

Additionally, *Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc.*, No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

Consequently, the scope of the instant claimed compositions, i.e. protein aggregates, includes an enormous number of structural variants.

In contrast, the instant specification provided a generic definition of the phrase "protein aggregates" (see specification pg. 7, lines 9-12) and a laundry list as to the type of protein that can be use in the instant claimed method (see specification pg. 10, lines 10-19). The instant specification one example is directed to the method of high-pressure refolding of the folding intermediates of a known protein, i.e. tailspike protein, to its native protein (i.e. '*a portion of the dissociated protein folding intermediates refolds to native protein*')(see specification Example 6,

pg. 21, lines 1-21). Moreover, the instant specification discloses that the tailspike protein of P22 bacteriophage is "*an excellent model system for aggregation because the structure is known, the folding and aggregation pathways are well characterized*". Thus, the instant specification one example utilizes a well-known protein in which the intermediate forms of the folding and aggregates pathway of the protein are known.

Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding adequate disclosure. For adequate disclosure, like enablement, requires ***representative examples***, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. In addition, when there is ***substantial variation within the genus***, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05).

Here, the instant specification has only provided one working example of the claimed invention (i.e. high-pressure refolding method of protein aggregates comprising '*protein folding intermediates of a native protein*' using a well known tailspike protein wherein the known intermediate forms of the folding and aggregates pathway of the protein are refolded to its native form). Thus, a person of skill in the art would not believe that Applicants were in possession of

a genus that encompasses virtually an infinite number of compounds and/or compositions encompassing every class and subclass of the instant claimed protein aggregates comprising '*protein folding intermediates of a native protein*'.

Accordingly, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention. The instant specification and claims do not provide any guidance as to what changes should be made to extend the instant specification one example to the infinite number of possibilities that are currently being claimed composition, i.e. protein aggregates comprising '*protein folding intermediates of a native protein*', for use in the instant claimed method. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variable, the instant specification single example is insufficient to describe the enormous genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the

claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In the present instance, the specification does not teach the instant claimed method using any protein aggregates comprising '*protein folding intermediates of a native protein*'. Therefore, only the method of high-pressure refolding of the folding intermediates of tailspike protein of P22 bacteriophage to its native protein, but not the full breadth of the claim method meet the written description provision of 35 U.S.C 112, first paragraph.

16. Claims7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of high-pressure refolding of the folding intermediates of a known protein, i.e. tailspike protein, to its native protein, does not reasonably provide enablement for the method of high-pressure refolding of the folding intermediates of any protein aggregates to its native protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is an enablement rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to: 1) The breadth of the claims; 2) The nature of the invention; 3) The state of the prior art; 4) The level of one of ordinary skill; 5) The level of predictability in the art; 6) The amount of direction provided by the inventor; 7) The presence or absence of working examples; and 8) The quantity

of experimentation necessary needed to make or use the invention based on the disclosure. (See *In re Wands* USPQ 2d 1400 (CAFC 1988)).

(1-2) The breadth of the claims and the nature of the invention:

The claims are drawn to a broad genus. Here, the instant invention claimed method uses a broad genus of compositions, i.e. protein aggregates comprising '*protein folding intermediates of a native protein*', which represents enormous scope because the claims do not place any limitations on the number of atoms, i.e. binding moieties, types of atoms or the way in which said atoms can be connected together to form such a compound and/or composition (protein structures). Thus, virtually an infinite number of possibilities would be included in Applicants' claimed scope encompassing virtually every known class and subclass of compounds (protein structures). For example, Lehninger et al. disclose each protein has a specific chemical or structural function such that each protein has a unique three-dimensional structure (pg. 160, lines 4-6; fig. 7-1). The three-dimensional structure of a protein is determined by its amino acid, but the relationship between the amino acid sequence and the three-dimensional structure is an intricate puzzle that has yet to be solved in detail (see pg. 160, lines 14-29). Thus, virtually an infinite number of possibilities would be included in Applicants' claimed scope encompassing virtually every known class and subclass of compounds, i.e. the protein structures of the folding and aggregates pathway for any protein. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art:

The art is unpredictable because while the methods for pressure denaturation of proteins are known at the time of filing such methods were not sufficiently routine or predictable at the time of filing, to permit one of skill in the art to devise strategies for the use of any protein aggregates such that '*a portion of the dissociated protein folding intermediates refolds to native protein*' at high pressure. For example, Panick et al. disclose the protein structure produced by pressure depends on the type of protein use as the starting material (see pg. 390, left col., line 40 thru right col., lines 19). Moreover, the nature of the transition state(s) in denaturalization of a protein may vary because '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure. For example, it is not known to what extent the structures of the heat and cold denatured proteins are similar. Moreover, our grasp of these possible differences depends upon the observable parameters used, and quantitative comparison of results between techniques is often difficult. Recognizing that the denatured state achieved by any perturbation method likely corresponds to a relatively large ensemble of conformations*' (see pg. 397, left col., line16 thru right col., line 6). Therefore, the art of denaturation of proteins is known to be difficult to optimize and/or correlates, especially when '*the structural properties of the denatured state achieved may depend upon the method employed to perturb the native structure*' (see pg. 397, left col., lines 16-18).

(4) The level of one of ordinary skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples:

Applicants have not provided one example is directed to the method of high-pressure refolding of the folding intermediates of a known protein, i.e. tailspike protein, to its native protein (i.e. '*a portion of the dissociated protein folding intermediates refolds to native protein*')(see specification Example 6, pg. 21, lines 1-21). Moreover, the instant specification discloses that the tailspike protein of P22 bacteriophage is "*an excellent model system for aggregation because the structure is known, the folding and aggregation pathways are well characterized*". Thus, the instant specification one example utilizes a well-known protein in which the intermediate forms of the folding and aggregates pathway of the protein are known.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Therefore based on the evidences as a whole regarding each of the above factors (e.g. factors 1-8), the specification, at the time the application was filed, does not satisfy the enablement requirement for the instant claimed method of high-pressure refolding of the folding intermediates for any protein aggregates to its native protein.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 3-5, 8, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The limitation of "*wherein said elevated hydrostatic pressure is insufficient to fully denature said protein*" of claims 3, 5, 8, and 11 is vague and indefinite because it is unclear as the metes and bound of the instant claimed "*elevated hydrostatic pressure*" that would not denature the instant claimed protein. The instant claimed specification disclosure recites the range of hydrostatic pressure, i.e. between about 0.5 kbar and 10 kbar, in which the protein of interest is subjected to 'high hydrostatic pressure' (see specification pg. 9, lines 9-12), but it is silent as to the 'high hydrostatic pressure' that would not denature the instant claimed protein. As a result, the instant claimed limitation of "*wherein said elevated hydrostatic pressure is insufficient to fully denature said protein*" of claims 3, 5, 8, and 11 is vague and indefinite, and claims 3, 5, 8, and 11 are rejected under 35 U.S.C. 112, second paragraph.

b. The limitation of "*a chaotropic agent in an amount which is insufficient to denature said native protein at ambient pressure*" of claims 4 and 10 is vague and indefinite because it is unclear as the metes and bound of the "*amount*" of chaotropic agent at ambient pressure that would not denature the native protein. The instant claimed specification disclosure recites that '*In certain instances, the presence modest amounts of SDS, protease inhibitors or chaotropic agents may facilitate the methods of the present invention*' (see specification pg. 11, line 29 thru pg. 12, line 2), but it is silent as to the "*amount*" of chaotropic agent at ambient pressure that would not denature the native protein. As a result, the instant claimed limitation of "*a chaotropic agent in an amount which is insufficient to denature said native protein at ambient pressure*" of claims 4 and 10 is vague and indefinite, and claims 4 and 10 and all its dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

20. Claims 1, 3-5, 7, 8, 10, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Gorovits et al. (*Biochemistry*, **4/28/1998**, 37(17), pgs. 6132-6135).

The instant invention recites a method for recovering native protein from a sample. The method comprises the step of a) obtaining a sample comprising protein aggregates; b) subjecting the sample of step (a) to elevated hydrostatic pressure, whereby a portion of protein dissociates from said protein aggregates; c) returning the sample of step (b) to ambient pressure, wherein a portion of the dissociated protein refold to native protein.

As claimed in claim 7, the protein aggregates comprises protein folding intermediates of a native protein, and the dissociated protein comprises protein folding intermediates.

Gorovits et al. demonstrate that high pressure can increase protein folding by reducing nonspecific aggregation (see Abstract; pg. 6132, right col., lines 9-13; pg. 6133, left col., lines 29-40). The method comprises the step of preparing a sample of native rhodanese in 3.9 M concentration of urea (refers to instant claimed chaotropic agent) wherein rhodanese forms a molten globule-like structure that has a high level of hydrophobic exposure and a considerable amount of secondary structure (refers to instant claimed protein aggregates comprising protein folding intermediates; instant claimed step (a); and instant claims 4, and 10); subjecting the rhodanese sample to pressure at 2 kbar such that protein intermediates precipitates, i.e. dissociates, (refers to instant claimed step (b); and instant claims 3, 5, 8, and 11); and reducing the pressure such that the rhodanese are refolded to its native form (refers to instant claimed step (c))(see e.g. pg. 6133, left col., lines 29-40; pg. 6133, right col., lines 4-8; pg. 6133, right col., line 26 thru pg. 6134, left col., lines 3; pg. 6134, left col., lines 12-15; pg. 6134, right col., lines 17-33). Therefore, the method of Gorovits et al. anticipates the presently claimed method.

21. Claims 1-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Randolph et al. (US Patent 6,489,450 B2) alone or as evidenced by Paladini et al. (*Biochemistry*, **1981**, 20(9), pgs. 2587-2593).

The instant invention recites a method for recovering native protein from a sample. The method comprises the step of a) obtaining a sample comprising protein aggregates; b) subjecting the sample of step (a) to elevated hydrostatic pressure, whereby a portion of protein dissociates from said protein aggregates; c) returning the sample of step (b) to ambient pressure, wherein a portion of the dissociated protein refold to native protein.

As claimed in claim 7, the protein aggregates comprises protein folding intermediates of a native protein, and the dissociated protein comprises protein folding intermediates.

Randolph et al. disclose methods for recovering a properly folded protein from mixtures containing aggregates or inclusion bodies containing the protein or from solutions containing protein in a denatured state (see e.g. Abstract; col. 3, lines 33-37). In general, the method comprises the step of applying elevated pressure to a mixture comprising protein aggregates or inclusion bodies (refers to instant claimed steps (a); and instant claims 2, 3, 8, and 9) in two stages wherein the first stage the elevated pressure causes disaggregation and in the second stage the mixture is incubated at the elevated pressure to permit refolding to its native structure, and reducing the pressure to atmospheric pressure whereby the mixture remained refolded in its native structure (see e.g. col. 3, line 66 thru col. 4, line 17; claim 1). In one embodiment, the method includes the addition of chaotropic agent at concentration at atmospheric pressure wherein the protein does not unfold (refers to instant claims 4-6 and 10-11)(see e.g. col. 3, lines 51-60; col. 9, lines 40-62; col. 11, lines 39-58; claim 4). In addition, the method of Randolph et al. suggests that at pressures between 1 kbar and 3kbar oligomeric proteins dissociate into subunit (see e.g. col. 8, lines 37-43) and as evidenced by Paladini et al. (see e.g. Abstract)(refers

to instant claimed step (b)). Therefore, the method of Randolph et al. anticipates the presently claimed method.

Conclusion

22. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 571-272-0810. The examiner can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

My-Chau T. Tran
June 24, 2006